REMARKS

Claims 28-31 are pending in this application. While the Office Action indicates that claims 20-31 have been rejected, claims 28-31 have been rejected by the Examiner in this case. Claims 28 and 30 have been amended. Claim 29 and 31 have been canceled. No new matter has been added by this amendment. Reconsideration is respectfully requested.

I. Double Patenting

Claims 30-31 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,587,288. It is suggested that the allowed species of SarR analog, specifically a species of SarA that shares amino acid sequence similarity with SarR, serves to bind SarA promoters to repress transcription of collagen adhesion, protein A and several other genes encoding extracellular proteases which are known to be Staphylococcal virulence factors as well as would form a heterodimer with SarA of a different amino acid sequence as allowed SarA, because SarA is known to form dimers in the native host bacteria. The Examiner suggests that the allowed species anticipates the claimed genus of SarR analogs based upon the functional characteristics recited in the claims. Applicants respectfully disagree with this rejection.

U.S. Patent No. 5,587,288 teaches at column 4 (lines 35-41) that the allowed species of sarA is necessary for optimal expression of *agr* genes. In contrast, page 32 (lines 22-25) of the instant specification teaches that SarR down-regulates *sarA* expression by binding to the *sarA* promoter to down-modulate *sarA*

transcription thereby decreasing expression of genes downstream of the *sarA* regulatory cascade (*e.g., agr* genes). In this regard, the specification teaches at pages 10-11 that analogs of sarR can be used to interfere with the sarA homodimer to repress the expression of *sarA*. Accordingly, in an earnest effort to clarify the instant invention, Applicants have amended the claims to indicate that the sarR analog inhibits the expression *sarA* in *Staphylococcus*. In light of this amendment, claim 31 has been canceled. Because the allowed species of sarA does not have this effect on *sarA* expression in *Staphylococcus*, this reference cannot be held to make obvious the instant invention. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

II. Objection to the Specification

The Examiner has objected to the specification because it contains embedded hyperlinks and/or other forms of browser-executable code. Specifically, the Examiner requires that the phrase www.tiger.org be removed from the specification. Applicants have made the appropriate amendment to the specification and therefore respectfully request that this objection be withdrawn.

III. Rejection of Claims under 35 U.S.C. §101

Claims 30-31 have been rejected under 35 U.S.C. 101 as being directed to compounds that have not been isolated and purified to show the "hand of man". It is suggested that this rejection can be obviated by amending the claims to recite the phrase "isolated and purified." Applicants have made the appropriate amendment to claim 30 and respectfully request that this rejection be withdrawn.

IV. Rejection of Claims under 35 U.S.C. §112

Claims 28-31 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. It is suggested that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor at the time the application was filed had possession of the invention. It is suggested that the instant claims are directed to compositions and methods that utilize SarR analogs, wherein SarR analogs are only functionally defined in the claims to evidence the ability to form heterodimers with SarA or bind to an SarA promoter to inhibit virulence determinant expression which encompass mutant genes and proteins of SarR and small molecules that mimic the functional characteristics of the mutant SarR genes or proteins. It is acknowledged that while the specification discloses SEQ ID NOs:1 and 2, the specification has not described through written description the highly variable genus of analog SarR genes, analog SarR polypeptides and functional equivalents of these in the form of small molecules. With the exception of the nucleic acids and polypeptides encoded by SEQ ID NOs 1 and 2 and polynucleotides present in specific strains of *S. epidermidis, haemolyticus* and *saprophyticus*, it is suggested that the skilled artisan cannot envision the detailed structure of what is encompassed by the SarR analogs that includes mutants, homolog, analog genes and proteins from any source or species of bacteria, as well as small molecule functional equivalents of the analog and mutant genes and proteins. Applicants respectfully traverse this rejection.

Applicants respectfully believe that this is an improper rejection. Claims pending in this case are drawn to methods for *screening* for lead compounds which inhibit the expression of *sarA* in *Staphylococcus*. The whole point of a screening assay is to use a defined end-point to identify useful compounds from a library of compounds. Applicants have appreciated that a SarR protein having an amino acid sequence comprising SEQ ID NO:1 forms a heterodimer with SarA thereby blocking SarA homodimer formation and subsequent *SarA* expression. In this regard, the instant claims employ SarR/SarA heterodimer formation as an end-point useful for identifying compounds that inhibit the expression of *sarA* in *Staphylococcus*. Applicants provide a crystal structure for a SarR homodimer, wherein Figure 11 depicts the amino acid residues involved in dimerization (labeled with an H) and DNA binding (labeled with a D) and the conservation of the these amino acid residues in SarR and SarA. See also pages 36-38. Based on this understanding of the structure of SarR and SarA, the instant specification provides a general description as to the how to use molecular modeling of a SarR protein having an amino acid sequence of SEQ ID NO:1 to design peptidomimetics which mimic the structure of the SarR, screen random peptide libraries, or screen commercially available libraries of chemicals from sources such as Merck, GlaxoWelcome, etc. See pages 11-13. Moreover, Applicants demonstrate SarR analogs from *S. epidermidis, S. haemolyticus* and *S. saprophyticus*. Accordingly, in an earnest effort the facilitate the prosecution of the present application, Applicants have amended the claims as supported by the specification to clarify that a SarR

analog is of a SarR protein having an amino acid sequence comprising SEQ ID NO:1.

Using the guidance provided in the specification, one of skill in the art could readily envision analogs of a SarR protein of SEQ ID NO:1 to be screened in the accordance with the instant methods because structure-based drug design and library screening were routine in the art at the time of filing of the instant application. For example, Tretiakova et al. ((2000) *Nat. Biotechnol.* 18:984-988; enclosed herewith) disclose rational design of cytotoxic T-cell inhibitors by modeling the interaction between CD8 and MHC class I and preparation and screening of peptide analogs to block protein associations. Accordingly, based upon the structural information for a SarR protein of SEQ ID NO:1 and guidance for carrying out screening assays, one of skill in the art would readily appreciate that Applicants were in possession of SarR analogs useful for screening to identify a lead compound which forms a heterodimer with the SarA protein. Thus, Applicants have met the written description requirement set forth under 35 U.S.C. 112, first paragraph. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Claims 30 and 31 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The Examiner suggests that while the disclosure is enabling for claims limited to SarR protein from *S. aureus, S. epidermidis, S. haemolyticus* and *S. saprophyticus,* no specific deletion, substitution or insertion or any combination thereof within the encoded SarR protein has been recited and a change in any amino acid could result in an unstable molecule as evidenced by the teachings of Creighton (1984) and Nosoh et al. (1991). It is suggested that one of skill in the art would be

required to perform undue experimentation to use any amino acid at any location to produce the desired SarR analog protein that would inhibit expression of Staphylococcal virulence determinants. Applicants respectfully traverse this rejection.

As indicated above, Applicants have provided the crystal structure of SarR and numerous SarR analogs from *S. epidermidis, S. haemolyticus* and *S. saprophyticus*. Further, since the publication of Creighton (1984) and Nosoh et al. (1991), significant advances have been made in predicting the effect that a mutation will have on protein stability. In this regard, Topham et al. ((1997) *Prot. Eng.* 10:7-21; enclosed herewith) teach that using only structural information derived from parent wild-type crystal structures on a combined set of 83 staphylococcal nuclease and 68 barnase mutants, a correlation of 0.80 in the predicted stability changes with experimental thermodynamic data could be achieved. Approximately 86% of the predictions were correctly classified as destabilizing or stabilizing. Accordingly, given the crystal structure of wild-type SarR and the identity of numerous SarR analogs, one of reasonable skill in the art could predictably make amino acid deletions, substitutions or insertions without affecting the stability of SarR and without undue experimentation in view of the teachings of Topham et al. Accordingly, given the level of one of ordinary skill and the predictability in the art of protein engineering, the specification provides sufficient guidance at the time of filing of the application for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

Claim 29 has also been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. It is suggested that the recitation of the term "fragment" includes a single nucleotide, wherein the claimed fragment is not identified by any specific structure and is not required to be a functional fragment that also evidences promoter activity. In light of the cancellation of claim 29 as indicated below, it is respectfully requested that this rejection be withdrawn.

V. Rejection of Claims under 35 U.S.C. §102

Claims 29-31 have been rejected under 35 U.S.C. §102(a) as being anticipated by Tegmark et al. (2000). It is suggested that Tegmark et al. teach a compound that inherently would function as a Staphylococcal accessory regulatory (sarR) analog, wherein Tegmark et al. isolated the sarR protein analog from *S. aureus* and name it "P13". The Examiner suggests that Tegmark et al. also disclose a method comprising the steps of obtaining a SarR analog, wherein the analog is considered to be a SarA homolog named SarH1 which functions to repress the SarA promoter of the hla locus; contacting the sarR analog with an SarA promoter (*e.g.*, hla, hld, spa, and ssp); and determining whether the SarA analog binds to a SarA promoter. In light of the cancellation of claim 29 as indicated below, Applicants believe that this rejection is moot. Therefore, it is respectfully requested that this rejection be withdrawn.

Claims 29-31 have also been rejected under 35 U.S.C. §102(b) as being anticipated by Manna et al. (1998) in light of evidence provided by Manna et al. (2001). The Examiner suggests that Manna et al. teach a compound that inherently would function as a SarR

analog, wherein Manna et al. isolated the SarR protein analog from *S. aureus* and named it a 12 kDa protein based upon binding to the SarA P2 promoter and suggested its biological function as a repressor. It is further suggested that this reference teaches the screening method of claim 29. Applicants respectfully disagree with this rejection. However, in an earnest effort to facilitate the prosecution of the present application, Applicants have canceled claim 29. It is therefore respectfully requested that this rejection be withdrawn.

Claims 28, 30-31 have been rejected under 35 U.S.C. 102(e) as being anticipated by Hurlbert et al. (U.S. Patent no. 6,699,662). It is suggested that Hurlbert et al. teach a compound that would function as a SarR analog that serves to inhibit SarA function and prevent the expression of Staphylococcal virulence factors. The Examiner suggests that Hurlbert et al. teach a mutant SarA protein that will bind to SarA but prevent binding the agr promoter region, due to "disruption of subunit interaction" through forming a heterodimer. It is suggested that Hurlbert et al. teach a second species of SarR analog which is an RNA inhibitor of SarA-agr promoter binding and has the sequence of gly-TTTCTTAACTA-lys, as well as an 18mer gly-TCCAATTTTTCTTAACTA-lys. The Examiner further suggests that Hurlbert et al. discloses a compound and method that comprises the steps of obtaining a SarA analog (*e.g.*, PNA inhibitors), contacting the SarR analog with SarA (*i.e.*, the PNA molecule can out compete SarA for binding to the DNA and form a protein-DNA comples), and determining whether the analog forms a heterodimer (*i.e.*, forms a protein-DNA complex, a type of

heterodimer) which results in inhibition of expression of virulence determinants. Applicants respectfully traverse this rejection.

MPEP 2131 states that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

While Hurlbert et al. teach inhibitors that block the binding of SarA to the agr locus, this reference does not teach or suggest a SarR analog of a SarR protein having an amino acid sequence comprising SEQ ID NO:1 or heterodimer formation of the SarR analog with SarA to inhibit the expression of *sarA* in *Staphylococcus*. Because this reference fails to teach each and every element of that which is claimed, this reference cannot be held to anticipate the present invention.

VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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